UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

DATE: 31-JAN-2008

SUBJECT: PP#2F06430. Novaluron on Cotton, Pome Fruits, and Potato. **Review of Amendment Dated 21-JUN-2006 Submitted in Response to HED's Memoranda of 22-MAR-2004.** Submission of Requested Poultry Feeding Study. MRID#: 46870601. DP#: 336897. Chemical#: 124002. Decision#: 368928. 40 CFR 180.598.

FROM: Sarah J. Levy, Chemist
Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509P)

THROUGH: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)

TO: John Hebert/Kable Davis, RM 07
Registration Division (RD) (7505P)

In conjunction with PP#2F06430, the Agency established the following permanent tolerances for residues of novaluron (*N*-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl] amino]carbonyl]-2,6-difluorobenzamide) *per se*:

Fruit, pome, group 11	2.0 ppm
Apple, wet pomace	8.0 ppm
Cotton, undelinted seed	0.6 ppm
Cotton, gin by-products	30 ppm
Vegetables, tuberous and corm, subgroup 1C	0.05 ppm
Cattle#, meat	0.60 ppm
Cattle#, meat byproducts, except liver and kidney	0.60 ppm
Cattle#, fat	11 ppm
Cattle#, liver	1.0 ppm
Cattle#, kidney	1.0 ppm
Hog, meat	0.01 ppm
Hog, meat byproducts	0.01 ppm

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Hog, fat	0.05 ppm
Milk	1.0 ppm
Milk, fat	20 ppm
Poultry, meat	0.03 ppm
Poultry, mbyp	0.04 ppm
Poultry, fat	0.40 ppm
Eggs	0.05 ppm

Cattle, goat, horse, and sheep

Registration of Rimon™ 10 EC (emulsifiable concentrate; EPA Reg. No. 66222-35) was conditional upon the submission of additional residue chemistry data (Memo, G. Kramer, 22-MAR-2004; DP#: 285474). The current amendment addresses residue chemistry deficiencies identified in HED's previous review (Memo, G. Kramer, 22-MAR-2004; DP#: 285474). Note that several of the deficiencies related to this petition were addressed in the following memorandum: G. Kramer, 10-MAY-2005; DP#: 315890.

Executive Summary of Chemistry Deficiencies

- Submission of an interference study and/or confirmatory method.

- Submission of additional storage stability data for the poultry feeding study.

Note to RD: The appropriate chemical name for novaluron is "*N*-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl]amino]carbonyl]-2,6-difluorobenzamide." HED recommends that 40 CFR 180.598 should be amended accordingly.

RECOMMENDATIONS

HED continues to recommend for a conditional registration of Rimon™, pending submission of an interference study and/or confirmatory method and additional storage stability data for the poultry feeding study. Based on the submitted feeding study, the existing egg tolerance should be increased to 0.07 ppm.

CONCLUSIONS

OPPTS 860.1340 Residue Analytical Methods - Plants

An interference study is still required to determine whether other pesticides registered on the same commodities interfere with the determination of novaluron; an interference study may be waived if a specific single-analyte confirmatory method is submitted.

860.1480 Meat, Milk, Poultry, and Eggs

HED requests additional storage stability data for the poultry feeding study.

DETAILED CONSIDERATIONS

Deficiency - OPPTS 860.1340 Residue Analytical Methods - Plants (from Memo, G. Kramer, 22-MAR-2004; DP#: 285474)

The proposed plant enforcement methods, GC/ECD and HPLC/UV, need to pass a PMV by ACL/BEAD before the methods can be deemed adequate for tolerance enforcement. In addition, the petitioner is required to submit radiovalidation and interference studies. Radiovalidation of the GC/ECD and HPLC/UV methods is required, using radiolabeled samples from the plant metabolism studies, in order to determine whether the methods adequately extract aged (weathered) residues of novaluron. An interference study is required to determine whether other pesticides registered on the same commodities interfere with the determination of novaluron; an interference study may be waived if a specific single-analyte confirmatory method is submitted.

Petitioner's Response: The petitioner submitted acceptable plant and livestock radiovalidation studies (MRID#s 45638304 and 46714901; See Memo, S. Levy, 23-AUG-2006; DP#: 325183). The radiovalidation data support the analytical methods as enforcement methods.

HED's Conclusion: The Analytical Chemistry Branch (ACB) has successfully completed the petition method validation (PMV) (Memo, S. Levy, 15-SEP-2004; DP#: 306998). However, an interference study and/or confirmatory method have not been submitted. **This deficiency remains partially resolved.**

Deficiency - OPPTS 860.1480 Meat, Milk, Poultry, and Eggs (from Memo, G. Kramer, 22-MAR-2004; DP#: 285474)

The petitioner has requested a waiver for the conduct of a poultry feeding study. Based on the maximum residues observed in the poultry metabolism study, quantifiable residues would be expected in a feeding study. HED thus requested that the petitioner submit a poultry feeding study.

Petitioner's Response: A protocol for the requested poultry feeding study was submitted by the petitioner and reviewed by HED (Memo, G. Kramer, 05-MAY-2005; DP#: 315891). The petitioner submitted a poultry feeding study (MRID#: 46870601) that was adequate to demonstrate the magnitude of novaluron residues in poultry commodities. However, sample storage intervals were not reported.

HED's Conclusion: HED previously recommended for the following poultry tolerances based on the results of a poultry metabolism study: fat - 0.40 ppm; meat byproducts - 0.04 ppm; meat - 0.03 ppm; egg – 0.05 ppm (Memo, S. Levy, 22-MAR-2004; DP#: 285474). The levels of novaluron in the poultry metabolism study were normalized to 1x and then multiplied by a factor of 10x to account for the longer duration of a feeding study.

Cotton is the only poultry feed item associated with the registered uses of novaluron. The reasonably balanced diet (RBD) of novaluron to poultry is presented in Table 1. This poultry dietary burden was calculated using the registered tolerance level for cotton, undelinted seed (0.60 ppm).

Table 1. Poultry Dietary Burden.

Feedstuff (Type)	Tolerance (ppm)	%Dry Matter[1]	%Diet[1]	Dietary Burden[2] (ppm)
cottonseed meal (PC)	0.60	89	20	0.12
Total dietary burden				**0.12**

[1] Table 1 (OPPTS Guideline 860.1000).
[2] Dietary Burden = [tolerance/% DM (cattle)] x %diet). Poultry diets are not corrected for %dry matter.

Poultry feeding study

46870601.der.wpd

Four groups of twelve laying hens each were dosed with novaluron at 0, 0.12, 0.36, and 1.2 ppm in the feed for 56/57 consecutive days. Following withdrawal of the test diet after 56/57 days, three satellite groups of 12 birds each were returned to the control diet for 14, 42, or 70 days, to measure the kinetics of depuration. Composite egg samples were collected on Days -1, 3, 7, 9, 15, 19, 23, 27, 30, 33, 37, 40, 44, 47, 51, and 54 for all four groups. Additional composite egg sampling was conducted on Days 1, 5, and 12 for the 1.2 ppm group (Group 4). Hens were sacrificed within 24 hours after the treatment, and composite samples of muscle, liver, kidney, skin (with attached fat), and abdominal fat were collected. The maximum dose tested thus appears to be 10X the dietary burden.

Samples were analyzed for residues of novaluron *per se* using a liquid chromatography with mass-spectrometric detection (LC/MSD) method. The method was validated with the analysis of egg and tissue samples fortified at 0.01-1.0 ppm. Concurrent method recoveries were also analyzed for egg and tissue samples fortified at 0.01-3.0 ppm. The validated limit of quantitation (LOQ) was 0.01 ppm in chicken egg and tissues. The limit of detection (LOD) was 0.5 ng/mL (equivalent to 0.0025 ppm in all matrix types). The maximum residues of novaluron in eggs and tissues are listed below in Table 2.

Table 2. Results of a Poultry Feeding Study with Novaluron.

Matrix	Maximum Residue Levels (ppm) by Feeding Level*		
	0.12 (ppm)	0.36 (ppm)	1.2 (ppm)
Eggs, Day 7	0.020	0.092	0.246
Eggs, Day 27	0.045	0.179	0.542
Eggs, Day 54	0.063	0.181	0.702
Muscle	0.014	0.031	0.160
Liver	0.034	0.096	0.364
Kidney	0.039	0.089	0.368
Skin + Attached fat	0.161	0.462	1.842
Abdominal fat	0.323	0.988	3.011

Conclusions: Based on the feeding study and the current MTDBs, HED concludes that the currently-established tolerance levels are sufficient; with the exception of eggs. The egg tolerance should be increased to 0.07 ppm.

The poultry feeding study will be classified as scientifically acceptable, pending submission of additional storage stability information. Sample storage intervals for poultry commodities were not reported, nor was it demonstrated that the storage interval for the residue samples was less than 1 month. Storage stability data for novaluron residues should be submitted that support the storage conditions and intervals of poultry egg and poultry skin/fat, muscle, liver, kidney, and abdominal fat tissue samples used in this study or the petitioner should demonstrate that the storage interval for the residue samples was less than one month. When the requested data and information has been submitted, HED will reassess the adequacy of the recommended livestock commodity tolerances. **This deficiency is partially resolved.**

ATTACHMENT

46870601.der.doc

RDI: G. Kramer (31-JAN-2008), RAB1 Chemists (30-JAN-2008)
S. Levy:S-10953:PM#1:(703)305-0783:7509P:RAB1

Novaluron/Rimon/PC Code 124002/Huntingdon Life Sciences Limited
DACO 7.5.1/OPPTS 860.1480/OECD IIA 6.4.1, 6.4.2 and IIIA 8.2, 8.4.1, 8.4.2
Livestock Feeding Study – Laying Hens

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)
Date: 31-JAN-2008

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)
Date: 31-JAN-2008

This data-evaluation record (DER) was originally prepared under contract by Versar, Inc. (6850 Versar Center, Springfield, VA 22151; submitted 10-MAY-2007). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46870601 Rodgers, M.H. (2006) Rimon--Residue Transfer Study – Accumulation and Depletion of Residues in Eggs and Tissue of Laying Hens. Lab Project ID: MAK/0900. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 167 pages.

EXECUTIVE SUMMARY:

Huntingdon Life Sciences Limited has submitted a poultry feeding study with novaluron. Four treatment groups of twelve laying hens each were dosed with novaluron at 0, 0.12, 0.36, and 1.2 ppm in the feed for 56/57 consecutive days. Following withdrawal of test diet after 56/57 days, three satellite groups of 12 birds each were returned to the control diet for 14, 42, or 70 days, to measure the kinetics of depuration. Composite egg samples were collected on Days -1, 3, 7, 9, 15, 19, 23, 27, 30, 33, 37, 40, 44, 47, 51, and 54 for all four groups. Additional composite egg sampling was conducted on Days 1, 5, and 12 for the 1.2 ppm group (Group 4). Hens were sacrificed within 24 hours after the treatment, and composite samples of muscle, liver, kidney, skin (with attached fat), and abdominal fat were collected.

Novaluron was extracted from eggs and tissue using acetonitrile (ACN). Clean-up was by liquid-liquid partition, using hexane. Quantitation was performed using liquid chromatography with mass-spectrometric detection (LC/MSD). The method was validated with the analysis of egg and tissue samples fortified at 0.01-1.0 ppm. Concurrent method recoveries were also analyzed for egg and tissue samples fortified at 0.01-3.0 ppm. The validated limit of quantitation (LOQ) was 0.01 ppm in chicken egg and tissues. The limit of detection (LOD) was 0.5 ng/mL (equivalent to 0.0025 ppm in all matrix types).

Storage intervals were not provided in the report. Storage stability data for novaluron in poultry egg and tissues samples are not available to support the storage intervals of egg and tissue samples used in this study.

Maximum residues of novaluron found in eggs, muscle, liver, kidney, skin (with attached fat), and abdominal fat were 0.702 ppm, 0.16 ppm, 0.364 ppm, 0.368 ppm, 1.842 ppm, and 3.011

ppm, respectively. Higher residues were seen in fatty tissues, consistent with novaluron's lipophilic nature.

Residues of novaluron in eggs reached a steady state at 19 days for Groups 2 and 3, but continued to fluctuate for Group 4, reaching a maximum at Day 44. Linear relationships were established between residue data in tissue samples and increasing dose groups. Lastly, residues in poultry eggs and tissues declined towards zero with time during the depuration period, when hens were returned to control diets.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the feeding study residue data are classified as scientifically acceptable, pending submission of additional storage stability data. Storage intervals were not provided in the report. Furthermore, it was not demonstrated that the storage interval for the residue samples was less than 1 month; therefore, storage stability data for novaluron to support the storage conditions and intervals of poultry egg and poultry skin/fat, muscle, liver, kidney, and abdominal fat tissue samples used in this study should be submitted.

The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 336897].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance, and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Novaluron belongs to a class of pesticide chemicals called benzoylphenyl ureas that are insect-growth regulators (IGR). IGRs slowly kill insects over a period of few days by disrupting the normal growth and development of immature insects. Novaluron acts as an insecticide mainly by ingestion, but has some contact activity. Tolerances have been established in 40 CFR §180.598 for plant and livestock commodities and are expressed in terms of novaluron *per se*. The chemical structure and nomenclature of Novaluron is listed in Table A.1. The physicochemical properties of the technical grade of Novaluron are presented in Table A.2.

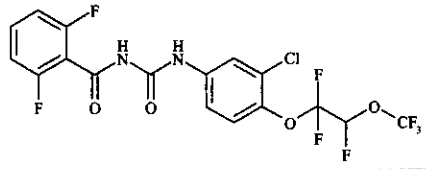
TABLE A.1. Test Compound Nomenclature.	
Compound	
Common name	Novaluron
Company experimental name	Rimon™
IUPAC name	1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea
CAS name	*N*-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl]amino] carbonyl]-2,6-difluorobenzamide
CAS registry number	116714-46-6
End-use product (EP)	Rimon™ 10 EC Insecticide (EPA Reg. No. 66222-35); Rimon™ 7.5 WDG Insecticide (EPA File Symbol No. 66222-LT)

TABLE A.2. Physicochemical Properties of the Technical Grade Test Compound: Rimon (Novaluron)		
Parameter	Value	Reference
Melting range	176.5 - 178.0 °C	449610-06
pH	6.5	449610-05
Density	1.56 g/cm^3 at 22 °C	449610-06
Water solubility	3 µg/L at 20 °C	449610-05 449610-06
Solvent solubility (at 25 °C)	8.39 mg/L in n-heptane 1.88 g/L in xylene 14.5 g/L in methanol 198 g/L in acetone 113 g/L in ethyl acetate 0.98 g/L in n-octanol	
Vapor pressure (mm Hg)	1.2 x 10^{-7}	449610-06
Dissociation constant, pK_a	Not determined due to low water solubility	449610-06
Octanol/water partition coefficient, Log(K_{OW})	4.3 at 25 °C	449610-06
UV/visible absorption spectrum	Molar absorption coefficients of at 3 maximum absorbances: 15,400 L/mol-cm at 253 µm (neutral) 9,780 L/mol-cm at 253 µm (acidic) 20,500 L/mol-cm at 263 µm (basic)	449610-06

B. EXPERIMENTAL DESIGN

The in-life phase of the study, including the formulation analysis, was conducted by Huntingdon Life Sciences, Ltd., Huntingdon Research Centre (Cambridgeshire, England). Domestic hens (*Gallus gallus domesticus*) of a laying strain were pre-acclimated for approximately 15 days. Bird selection for the study was based on clinical health and laying condition. The hens were randomly allocated to pens of 12 birds (*i.e.* 3 subgroups per treatment group). Spare birds were maintained under the same conditions as the test birds for use as possible replacements during

the pre-treatment period. On a weekly basis, the required amount novaluron was dissolved in acetone until a solution was obtained. The solution was added to a small quantity of plain diet and the solvent removed using a rotary evaporator at a temperature of 40°C. This mixture was gradually mixed with plain diet to achieve the final weight and blended in a mixer. Diet inclusion rates were 0.12 (Group 2), 0.36 (Group 3), and 1.2 (Group 4) ppm a.i. The test diets were offered *ad libitum* continuously as the only feed source for 8 weeks (56/57 days to Groups 2, 3, and 4a; 56 days to Groups 4b, 4c, and 4d). Following withdrawal of test diet after 56 days, birds in Groups 4b, 4c, and 4d were moved to clean floor pens and offered untreated feed *ad libitum* for 14, 42, or 70 days, respectively, to measure the kinetics of depuration. In confirmatory analysis of the treated feed, the mean concentrations of novaluron technical in test formulations were within ±20% of nominal concentrations, confirming accurate formulation.

B.1. Livestock

TABLE B.1.1. Description of Livestock Used in the Feeding Study.

Species	Strain	Age	Weight at study initiation (kg)	Health status	Description of housing/holding area
Laying hens (*Gallus gallus domesticus*)	Hi Line	38 weeks	1.49-2.17	Healthy	Group-housed in galvanized steel pens with concrete floors with wood shavings as litter; temperature 19-22°C; humidity 41-49%, artificial lighting provided 17 hours of light/day.

TABLE B.1.2. Test Animal Dietary Regime.

Composition of Diet	Feed consumption (kg/hen/day)	Water	Acclimation period	Predosing
Meal (Special Diets Services, Witham, Essex, UK) *ad libitum*	0.089-0.133 (average)	*ad libitum*	15 days	none

TABLE B.1.3. Dosing Regime.

Treatment group[1]	Treatment Type	Average daily administered dose (ppm-day)[2]	Residue intake in diet (ppm)	Vehicle	Timing/Duration
1	Oral	0	0.0	Feed	Continuous feeding for 56 or 57 consecutive days
2		0.0077	0.12		
3		0.0244	0.36		
4A		0.0754	1.2		
4B		0.0844	1.2		
4C		0.0776	1.2		
4D		0.0779	1.2		

[1] Group 1 received untreated feed; each group consisted of 3 subgroups of 4 birds.
[2] Calculated by the petitioner based on the group average feed consumption and group average body weight.

TABLE B.1.4. Sample Collection.				
Eggs collected	Number of eggs produced during normal production	Urine, feces and cage wash collected	Interval from last dose to sacrifice (hours)	Tissues harvested and analyzed
At least 2x daily	Hens produced one egg per day or every other day. The weights of the subsamples for each pen were recorded.	Not collected	24	Skin + attached fat, abdominal fat, skeletal muscle (breast/ thigh combined), liver, and kidneys

B.2. Sample Handling and Preparation

All eggs produced from Day 1 to termination were collected and wiped with a clean damp towel. Composite egg samples were collected on Days -1, 3, 7, 9, 15, 19, 23, 27, 30, 33, 37, 40, 44, 47, 51, and 54 for Groups 1, 2, 3, and 4. Additional composite egg sampling was conducted on Days 1, 5, and 12 for Group 4. Composite egg samples were derived by randomly dividing each group into 3 subgroups. The egg contents (whites and yolks combined, shells discarded) were pooled within subgroups to give 3 unique composite samples per group; these were weighed for future possible use. Each subgroup sample was then further divided into two subsamples and stored in suitably labeled plastic containers. Soft shelled or broken eggs were removed and discarded and excluded from the sampling procedures. All egg samples were stored at -20°C.

At termination, composite tissue samples of skeletal muscle (breast/thigh combined), liver, kidneys, skin and underlying subcutaneous fat, and abdominal fat were collected. For each subgroup of four birds, the tissues were pooled to give three pooled samples of each tissue per treatment group. These were then washed, weighed, coarsely chopped and mixed, and subdivided to give duplicate subsamples. All tissue samples were stored in plastic bags and frozen at -20°C.

One complete set of egg subsamples and one complete set of subsamples of pooled tissues were sent for analysis at Huntingdon Life Sciences Department of Residue Analysis (Eye Research Centre). Upon receipt at Huntingdon Life Sciences Department of Residue Analysis, all samples were placed in freezer storage. Tissue samples were transferred individually from freezer storage and processed from frozen by homogenization with dry ice using a homogenizer or commercial blender (or equivalent). Samples were returned to freezer storage after processing and left to allow sublimation of dry ice. The second set of subsamples of eggs and tissues were retained frozen at Huntingdon Life Sciences as reserve samples in case of loss or reassay.

B.3. Analytical Methodology

Residues of novaluron were extracted from egg and tissues (kidney, liver, muscle, abdominal fat and subcutaneous fat) using ACN. Clean-up was by liquid-liquid partition, using hexane. Quantitation was performed using LC/MSD.

The method was validated with the analysis of egg and tissue samples using samples from undosed hens fortified with each analyte at 0.01-1.0 ppm. The validated LOQ was 0.01 ppm in chicken egg and tissues. The LOD was 0.5 ng/mL (equivalent to 0.0025 ppm in all matrix types).

C. RESULTS AND DISCUSSION

Sample storage conditions are summarized in Table C.2. Storage intervals were not reported.

The method of analysis was validated on one occasion for each matrix. Samples were validated in the range 0.01 to 1.0 ppm. The average method recoveries for novaluron ranged from 84% to 110% (average of 102% with a standard deviation of 7.5%, n= 10) for eggs, 93% to 109% (average of 101% with a standard deviation of 5%, n =10) for muscle, 85% to 109% (average of 99% with a standard deviation of 7%, n=10) for liver, 96% to 109% (average of 102% with a standard deviation of 5.2%, n=10) for kidney, 83% to 105% (average of 95% with a standard deviation of 7.3%, n =10) for skin and attached fat, and 89% to 110% (average of 101% with a standard deviation of 7.5%, n=10) for abdominal fat.

Concurrent method recovery data are presented in Table C.1. The overall average concurrent recoveries for novaluron were as follows: for egg samples, fortified from 0.01 to 1.0 ppm, recoveries ranged from 70.0% to 110% (average of 92.2% with a standard deviation of 9.9%, n=49); for liver and kidney samples, fortified at 1.0 ppm, recoveries ranged from 91.2% to 103% (average of 95.0% with a standard deviation of 5.1%, n =4); for skin/attached fat and abdominal fat, fortified at 1.0 ppm, recoveries ranged from 101% to 109% (average of 104% with a standard deviation of 3.5%, n=4); for muscle, fortified at 1.0 ppm, recoveries ranged from 93.2% to 95.4% (average of 94.3%, n=2); and for tissue, fortified from 0.01 to 3.0 ppm, recoveries ranged from 69.8% to 110% (average of 90.9% with a standard deviation of 13.5%, n =15).

The fortification levels encompass the observed residue levels found in egg and tissue samples. Chromatograms of control samples appear to be free from interferences. The method was adequate for data collection based on acceptable method validation and concurrent method recoveries.

The results of the feeding study are reported in Table C.3 and a summary of residues of novaluron in eggs and poultry tissues at 0.12 ppm, 0.36 ppm, and 1.2 ppm feeding levels are presented in Table C.4. Following dosing at 0.12, 0.36, and 1.2 ppm, residues of novaluron were:

- 0.016 to 0.063 ppm, 0.036 to 0.181 ppm, and 0.109 to 0.702 ppm, respectively, in eggs;
- 0.010 to 0.014 ppm, 0.024 to 0.031 ppm, and 0.089 to 0.160 ppm, respectively, in muscle;
- 0.030 to 0.034 ppm, 0.087 to 0.096 ppm, and 0.273 to 0.364 ppm, respectively, in liver;
- 0.031 to 0.039 ppm, 0.080 to 0.089 ppm, and 0.250 to 0.368 ppm, respectively, in kidney;
- 0.125 to 0.161 ppm, 0.423 to 0.462 ppm, and 1.331 to 1.842 ppm, respectively, in skin and attached fat; and

- 0.278 to 0.323 ppm, 0.807 to 0.988 ppm, and 2.307 to 3.011 ppm, respectively, in abdominal fat.

Higher residues were seen in fatty tissues, consistent with novaluron's lipophilic nature (ranking from highest to lowest residues: abdominal fat > skin/fat > liver, kidney > muscle).

Residues of novaluron in eggs reached a steady state at 19 days for Groups 2 and 3, while they continued to fluctuate for Group 4, reaching a maximum at Day 44 (Figure C.1). Muscle, liver, kidney, skin/fat, and abdominal fat residues all showed an increasing linear relationship between residue levels and dose groups (Figure C.2). Lastly, residues in poultry eggs and tissues treated at the highest dose level declined towards zero with time during the depuration period, when hens were returned to control diets (Table C.5 and Figure C.3).

TABLE C.1. Summary of Concurrent Recoveries of Novaluron from Poultry Eggs and Tissues.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev* (%)	Overall Mean ± std dev* (%)
Eggs	0.01	1	85.0	85.0	92.2 ± 9.9
	0.1	11	70.0, 77.5, 82.5, 84.0, 84.2, 86.5, 87.4, 87.7, 89.4, 100, 110	87.2 ± 10.6	
	0.5	1	100	100	
	1.0	36	72.4, 74.2, 75.5, 76.8, 82.4, 84.4, 87.8, 88.0, 89.0, 89.7, 89.7, 90.1, 90.2, 92.1, 93.2, 93.8, 93.8, 95.1, 95.2, 95.3, 95.7, 96.4, 96.7, 96.8, 98.1, 98.4, 101, 102, 102, 102, 102, 103, 105, 109, 109, 109	93.7 ± 9.5	
Muscle	1.0	2	93.2, 95.4	94.3	94.3
Liver	1.0	2	91.2, 93.3	92.2	92.2
Kidney	1.0	2	92.9, 103	97.7	97.7
Skin/Attached fat	1.0	2	101, 102	102	102
Abdominal Fat	1.0	2	102, 109	106	106
Tissue	0.1	10	69.8, 71.0, 83.5, 84.6, 86.1, 88.1, 95.0, 99.5, 100, 110	88.8 ± 12.8	90.9 ± 13.5
	1.0	3	70.7, 92.2, 110	91.0 ± 19.8	
	3.0	2	100, 103	101	

* Standard deviations for mean values were not calculated where the number of individual values used to calculate the mean was less than three.

TABLE C.2. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration (days)	Interval of Demonstrated Storage Stability (days)
Eggs	-20	Not Reported	No poultry egg or tissue storage stability studies are available for novaluron.
Muscle		Not Reported	
Liver		Not Reported	
Kidney		Not Reported	
Skin + attached fat		Not Reported	
Abdominal fat		Not Reported	

TABLE C.3. Residue Data from Poultry Feeding Study with Novaluron.

Matrix	Collection Time	Group Residues (ppm)						
		1 (control)	2 (0.12)	3 (0.36)	4a (1.2)	4b (1.2)	4c (1.2)	4d (1.2)
Eggs	Day -1	ND	ND	ND	ND	ND	ND	ND
		ND	ND	ND	ND	ND	ND	ND
		ND	ND	ND	ND	ND	ND	ND
	Day 1	NA	NA	NA	ND	ND	ND	ND
		NA	NA	NA	ND	ND	ND	ND
		NA	NA	NA	ND	ND	ND	ND
	Day 3	ND	<0.01	0.011	0.023	0.016	0.042	0.023
		ND	<0.01	0.014	0.022	0.043	0.026	0.018
		ND	<0.01	<0.01	0.031	0.046	0.020	0.013
	Day 5	NA	NA	NA	0.063	0.085	0.087	0.068
		NA	NA	NA	0.074	0.060	0.117	0.051
		NA	NA	NA	0.068	0.126	0.123	0.041
	Day 7	ND	0.016	0.066	0.109	0.195	0.214	0.206
		ND	0.020	0.036	0.163	0.204	0.169	0.209
		ND	0.019	0.092	0.210	0.192	0.205	0.246
	Day 9	ND	0.022	0.087	0.252	0.297	0.212	0.251
		ND	0.024	0.095	0.218	0.208	0.224	0.211
		ND	0.024	0.073	0.234	0.267	0.248	0.199
	Day 12	NA	NA	NA	0.222	0.272	0.273	0.322
		NA	NA	NA	0.288	0.382	0.250	0.298
		NA	NA	NA	0.284	0.239	0.271	0.301
	Day 15	ND	0.041	0.084	0.407	0.442	0.460	0.328
		ND	0.054	0.124	0.398	0.322	0.327	0.236
		ND	0.039	0.114	0.282	0.373	0.389	0.456
	Day 19	ND	0.052	0.155	0.624	0.589	0.533	0.471
		ND	0.056	0.192	0.719	0.394	0.501	0.508
		ND	0.045	0.217	0.598	0.329	0.551	0.459
	Day 23	ND	0.060	0.160	0.595	0.584	0.584	0.483
		ND	0.054	0.174	0.549	0.527	0.448	0.547
		ND	0.049	0.187	0.596	0.483	0.525	0.502
	Day 27	ND	0.036	0.179	0.486	0.435	0.397	0.362
		ND	0.044	0.112	0.318	0.387	0.372	0.500
		ND	0.045	0.125	0.358	0.388	0.379	0.542
	Day 30	ND	0.045	0.121	0.582	0.492	0.349	0.517
		ND	0.040	0.114	0.479	0.455	0.458	0.409
		ND	0.046	0.120	0.626	0.509	0.533	0.478
	Day 33	ND	0.051	0.106	0.508	0.943	0.368	0.421
		ND	0.055	0.256	0.501	0.495	0.559	0.339
		ND	0.047	0.152	0.503	0.463	0.338	0.450
	Day 37	ND	0.037	0.111	0.379	0.332	0.288	0.324
		ND	0.029	0.108	0.452	0.437	0.471	0.325
		ND	0.042	0.123	0.429	0.373	0.328	0.449
	Day 40	ND	0.030	0.102	0.356	0.505	0.750	0.761
		ND	0.046	0.152	0.856	0.544	0.641	0.522
		ND	0.037	0.152	0.575	0.407	0.400	0.571
	Day 44	ND	0.053	0.160	0.585	0.662	0.431	0.473
		ND	0.049	0.135	0.706	0.564	0.579	0.500
		ND	0.062	0.173	0.606	0.690	0.669	0.571

TABLE C.3. Residue Data from Poultry Feeding Study with Novaluron.

Matrix	Collection Time	Group Residues (ppm)						
		1 (control)	2 (0.12)	3 (0.36)	4a (1.2)	4b (1.2)	4c (1.2)	4d (1.2)
	Day 47	ND	0.067	0.180	0.486	0.547	0.563	0.599
		ND	0.064	0.167	0.559	0.796	0.579	0.504
		ND	0.080	0.175	0.726	0.496	0.602	0.326
	Day 51	ND	0.035	0.117	0.336	0.374	0.395	0.379
		ND	0.040	0.103	0.343	0.437	0.524	0.357
		ND	0.034	0.117	0.629	0.340	0.439	0.491
	Day 54	ND	0.041	0.122	0.702	0.613	0.492	0.359
		ND	0.063	0.181	0.612	0.660	0.532	0.431
		ND	0.050	0.180	0.471	0.591	0.368	0.475
Muscle	Sacrifice	ND	0.01	0.031	0.101			
		ND	0.012	0.031	0.16	NA	NA	NA
		ND	0.014	0.024	0.089			
Liver	Sacrifice	ND	0.03	0.094	0.312			
		ND	0.034	0.096	0.364	NA	NA	NA
		ND	0.034	0.087	0.273			
Kidney	Sacrifice	ND	0.037	0.08	0.284			
		ND	0.039	0.088	0.368	NA	NA	NA
		ND	0.031	0.089	0.25			
Skin + attached fat	Sacrifice	ND	0.125	0.462	1.665			
		ND	0.144	0.436	1.842	NA	NA	NA
		ND	0.161	0.423	1.331			
Abdominal fat	Sacrifice	ND	0.278	0.897	2.882			
		ND	0.323	0.988	3.011	NA	NA	NA
		ND	0.321	0.807	2.307			

Notes: LOQ = 0.01 ppm.
LOD = 0.5 ng/mL (0.0025 ppm).
ND = Not detected (<LOD), NA = Not Analyzed.

TABLE C.4. Summary of Residue Data from Poultry Feeding Study with Novaluron.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)					
		n	Min.	Max.	Median	Mean	Std. Dev.
Eggs, Day 7	0.12	3	0.016	0.020	0.019	0.018	0.002
Eggs, Day 27		3	0.036	0.045	0.044	0.042	0.005
Eggs, Day 54		3	0.041	0.063	0.05	0.051	0.011
Muscle		3	0.010	0.014	0.012	0.012	0.002
Liver		3	0.030	0.034	0.034	0.033	0.002
Kidney		3	0.031	0.039	0.037	0.036	0.004
Skin + attached fat		3	0.125	0.161	0.144	0.143	0.018
Abdominal fat		3	0.278	0.323	0.321	0.307	0.025
Eggs, Day 7	0.36	3	0.036	0.092	0.066	0.065	0.028
Eggs, Day 27		3	0.112	0.179	0.125	0.139	0.036
Eggs, Day 54		3	0.122	0.181	0.18	0.161	0.034
Muscle		3	0.024	0.031	0.031	0.029	0.004
Liver		3	0.087	0.096	0.094	0.092	0.005
Kidney		3	0.080	0.089	0.088	0.086	0.005
Skin + attached fat		3	0.423	0.462	0.436	0.440	0.020
Abdominal fat		3	0.807	0.988	0.897	0.897	0.091

TABLE C.4. Summary of Residue Data from Poultry Feeding Study with Novaluron.

Matrix	Feeding Level (ppm)	Residue Levels (ppm)					
		n	Min.	Max.	Median	Mean	Std. Dev.
Eggs, Day 7	1.2	12	0.109	0.246	0.205	0.194	0.034
Eggs, Day 27		12	0.318	0.542	0.388	0.410	0.067
Eggs, Day 54		12	0.359	0.702	0.512	0.526	0.112
Muscle		3	0.089	0.160	0.101	0.117	0.038
Liver		3	0.273	0.364	0.312	0.316	0.046
Kidney		3	0.250	0.368	0.284	0.301	0.061
Skin + attached fat		3	1.331	1.842	1.665	1.613	0.259
Abdominal fat		3	2.307	3.011	2.882	2.733	0.375

FIGURE C.1. Novaluron Residues in Eggs as a Function of Time. Residues are average values for each treatment group.

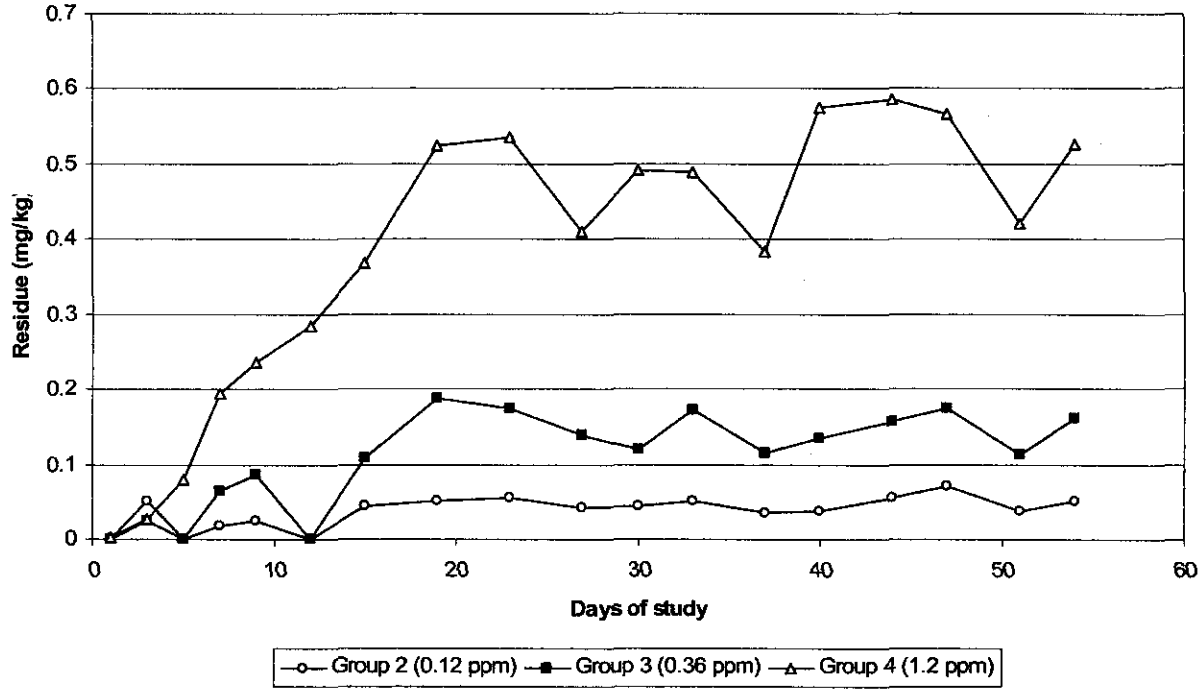
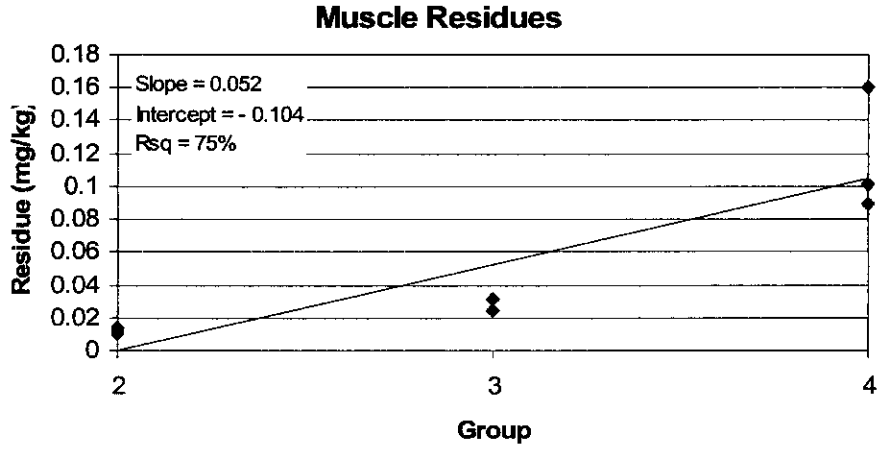
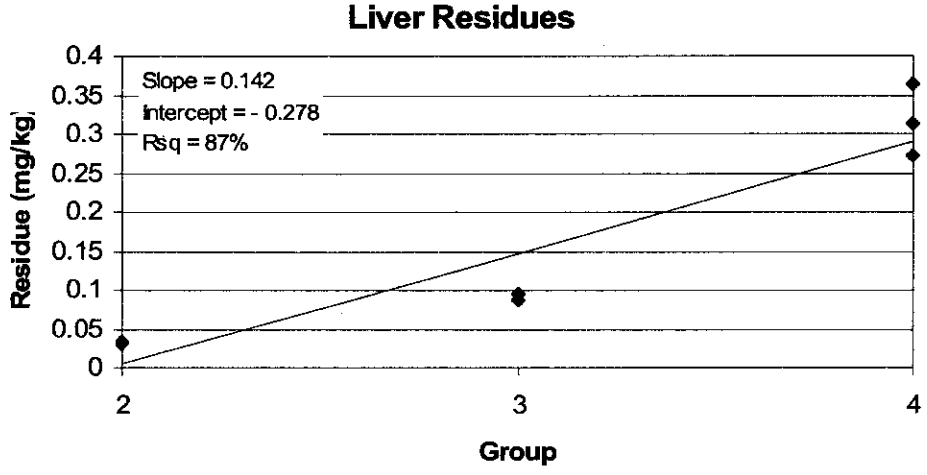
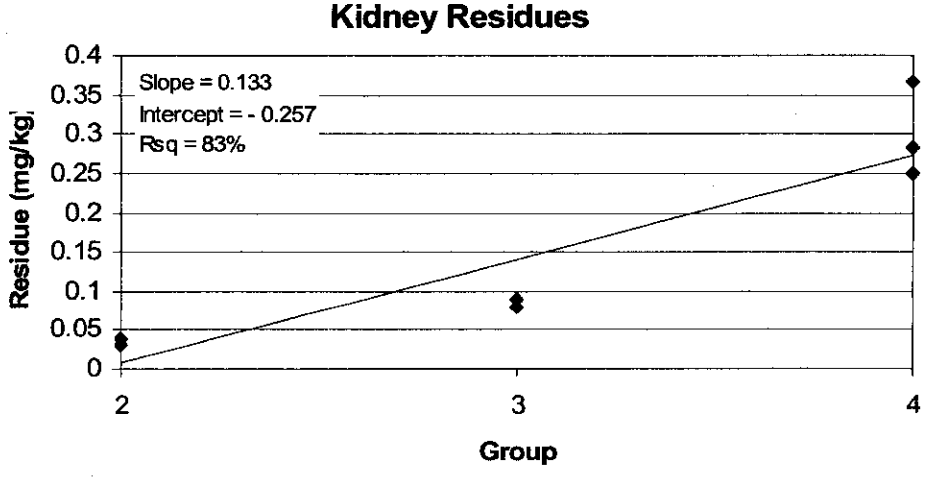
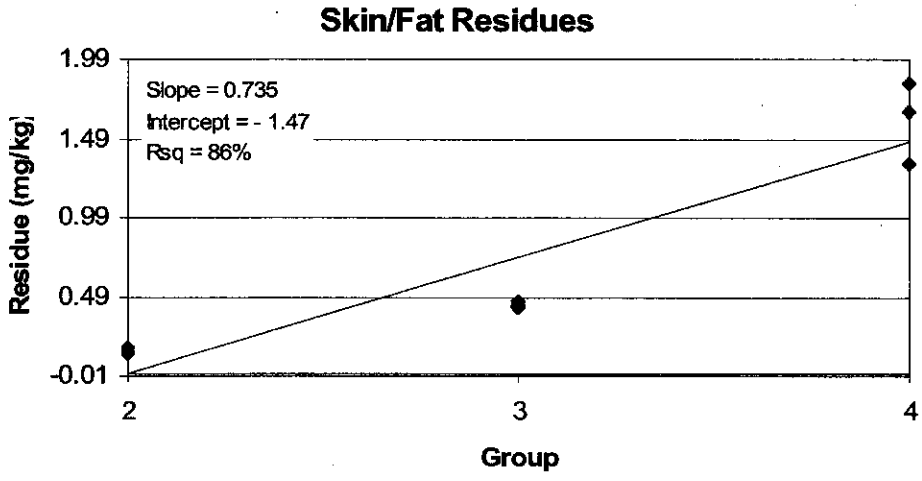


FIGURE C.2. Linear Regression of Residues on Feeding Level.








Skin/Fat Residues
Slope = 0.735
Intercept = - 1.47
Rsq = 86%
Residue (mg/kg)
1.99
1.49
0.99
0.49
-0.01
2
3
4
Group

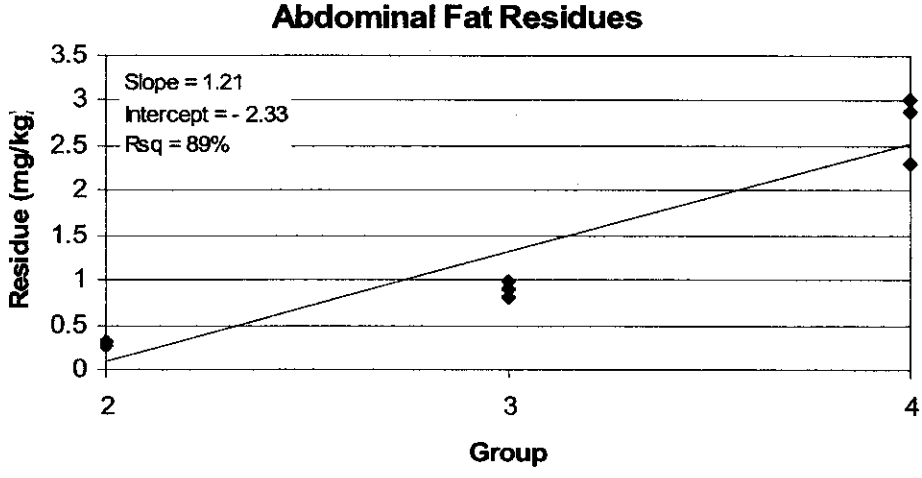
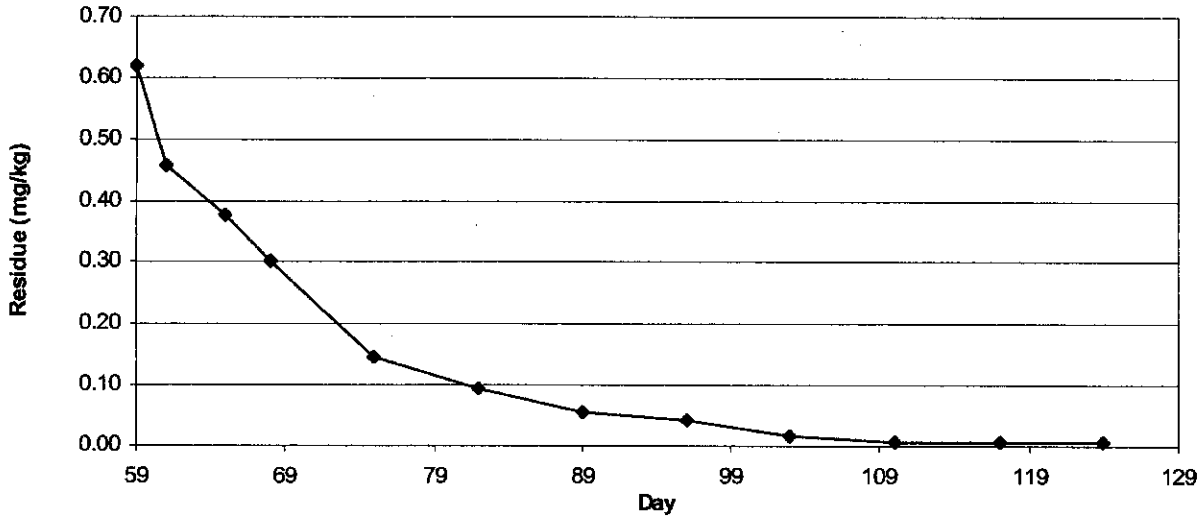

Abdominal Fat Residues
Slope = 1.21
Intercept = - 2.33
Rsq = 89%
Residue (mg/kg)
3.5
3
2.5
2
1.5
1
0.5
0
2
3
4
Group

TABLE C.5. Summary of Novaluron Residues in Eggs and Tissues of Poultry from the Depuration Study.

Matrix	Study Day	Group Residues* (ppm)	Mean ± std dev
Eggs	54	0.359, 0.368, 0.431, 0.471, 0.475, 0.492, 0.532, 0.591, 0.612, 0.613, 0.660, 0.702	0.53 ± 0.11
	59	0.518, 0.521, 0.541, 0.597, 0.606, 0.631, 0.681, 0.702, 0.76	0.62 ± 0.085
	61	0.156, 0.339, 0.409, 0.449, 0.451, 0.519, 0.532, 0.6, 0.645	0.46 ± 0.147
	65	0.313, 0.332, 0.346, 0.354, 0.382, 0.401, 0.407, 0.428, 0.431	0.38 ± 0.043
	68	0.252, 0.256, 0.278, 0.286, 0.289, 0.32, 0.323, 0.35, 0.351	0.30 ± 0.037
	75	0.081, 0.085, 0.118, 0.18, 0.203, 0.209	0.15 ± 0.058
	82	0.074, 0.082, 0.083, 0.094, 0.101, 0.134	0.09 ± 0.025
	89	0.034, 0.035, 0.045, 0.062, 0.077, 0.077	0.06 ± 0.020
	96	0.019, 0.028, 0.048, 0.05, 0.051, 0.057	0.04 ± 0.015
	103	0.013, 0.014, 0.019	0.02 ± 0.003
	110	< LOQ, < LOQ, 0.013	< LOQ
	117	< LOQ, < LOQ, < LOQ	< LOQ
	124	< LOQ, < LOQ, < LOQ	< LOQ
Muscle	57	0.089, 0.101, 0.160	0.12 ± 0.038
	71	0.034, 0.4, 0.46	0.04 ± 0.006
	99	< LOQ, < LOQ, < LOQ	< LOQ
	127	ND, ND, < LOQ	< LOQ
Liver	57	0.273, 0.312, 0.364	0.32 ± 0.046
	71	0.065, 0.078, 0.081	0.075 ± 0.009
	99	< LOQ, < LOQ, 0.023	0.011 ± 0.01
	127	< LOQ, < LOQ, < LOQ	< LOQ
Kidney	57	0.250, 0.284, 0.368	0.30 ± 0.061
	71	0.08, 0.089, 0.116	0.095 ± 0.019
	99	< LOQ, < LOQ, 0.03	0.013 ± 0.014
	127	< LOQ, < LOQ, < LOQ	< LOQ
Skin/Fat	57	1.331, 1.665, 1.842	1.61 ± 0.259
	71	0.332, 0.505, 0.694	0.51 ± 0.181
	99	0.043, 0.072, 0.16	0.092 ± 0.061
	127	< LOQ, < LOQ, 0.01	< LOQ
Abdominal Fat	57	2.307, 2.882, 3.011	2.733 ± 0.375
	71	1.121, 1.181, 1.258	1.187 ± 0.069
	99	0.143, 0.17, 0.341	0.218 ± 0.107
	127	0.01, 0.018, 0.023	0.017 ± 0.007

* Depuration analyses only conducted on highest dose group (1.2 ppm).

FIGURE C.3. Depuration curve for residues of Novaluron in Eggs.



D. CONCLUSION

The submitted poultry feeding study is adequate to demonstrate the magnitude of residues of novaluron in/on poultry commodities, pending submission of additional storage stability data. Storage intervals were not provided in the report. Furthermore, it was not demonstrated that the storage interval for the residue samples was less than 1 month; therefore, storage stability data for novaluron to support the storage conditions and intervals of poultry egg and poultry skin/fat, muscle, liver, kidney, and abdominal fat tissue samples used in this study should be submitted.

Maximum residues found in eggs, muscle, liver, kidney, skin (with attached fat), and abdominal fat were 0.702 ppm, 0.16 ppm, 0.364 ppm, 0.368 ppm, 1.842 ppm, and 3.011 ppm, respectively. Higher residues were seen in fatty tissues, consistent with novaluron's lipophilic nature. Residues of novaluron in eggs reached a steady state at 19 days for Groups 2 and 3, but continued to fluctuate for Group 4, reaching a maximum at Day 44. Linear relationships were established between residue data in tissue samples and increasing dose groups. Lastly, residues in poultry eggs and tissues declined towards zero with time during the depuration period, when hens were returned to control diets.

E. DOCUMENT TRACKING

RDI: G.F. Kramer (31-JAN-2008), RAB1 Chemists (30-JAN-2008)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
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Chemical:	**Novaluron**
	PC Code: 124002
HED File Code:	**11000 Chemistry Reviews**
Memo Date:	**1/31/2008**
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	DPD315890
	DPD325183
	DPD306998
	DPD315891
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